

Immunogenicity and safety results from a randomized multicenter trial comparing a Tdap-IPV vaccine (REPEVAX®) and a tetanus monovalent vaccine in healthy adults

New considerations for the management of patients with tetanus-prone injuries

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Keywords: immunogenicity, injuries, REPEVAX®, safety, Tdap-IPV vaccine, tetanus toxoid

Abbreviations: BMI, body mass index; CI, confidence interval; eCRF, electronic case report form; ELISA, enzyme-linked immunosorbent assay; GMC, geometric mean concentration; GMCR, geometric mean of individual concentration ratio; PP, per protocol; TMV, tetanus monovalent vaccine

In adults with a tetanus-prone injury, combined vaccines such as Tdap-IPV (REPEVAX®) can boost immunity against several diseases simultaneously. This phase IIIb, parallel-group, open-label trial compared antibody responses to Tdap-IPV and tetanus monovalent vaccine (TMV; Vaccin Tétanique Pasteur® or Tetavax®) against tetanus toxoid 10 and 28 days post-vaccination. Between July and December 2009, four centers in France and five in Germany recruited healthy adults who had received a tetanus-containing vaccine 5–10 years previously. Participants were randomized 1:1 to receive at the first visit a single dose (0.5 mL) of Tdap-IPV or TMV, with follow-up visits at Day 10 and Day 28. Outcomes: per protocol (PP) population immunogenicity at Day 10 (primary) and at Day 28 (secondary); safety throughout the study. Of 456 adults randomized, 223 received Tdap-IPV and 233 received TMV (PP population: 183 and 199 participants, respectively). All participants receiving Tdap-IPV and 99.0% receiving TMV had an anti-tetanus antibody concentration ≥ 0.1 IU/mL, confirming non-inferiority of Tdap-IPV to TMV (95% confidence interval of the difference: -1.2, 3.6). Number of adverse events reported was comparable in each group. Injection-site reactions were reported by 76.6% participants receiving Tdap-IPV and 74.6% receiving TMV. Systemic events (e.g., malaise, myalgia and headache) were reported in 47.7% and 39.7% of the Tdap-IPV and the TMV groups, respectively. Tdap-IPV is effective and well-tolerated for use in the management of tetanus-prone injuries in emergency settings in persons for whom a booster against diphtheria, pertussis and poliomyelitis is also needed. ClinicalTrials.gov identifier: NCT00928785. Research sponsored by Sanofi Pasteur MSD.

Introduction

Booster vaccinations are recommended throughout life to maintain protection against communicable diseases in the general population. However, compliance with vaccine programmes among adults is low, perhaps because of the misperception that booster vaccinations are unnecessary, leading to low vaccine coverage rates.^{1,2} Consequently, adults may become more susceptible

to common childhood diseases such as diphtheria, pertussis and poliomyelitis and to tetanus in the case of a wound or injury.

In 2002, the total number of deaths worldwide caused by tetanus was estimated at around 213,000,³ most of which were reported in developing countries and at least half in neonates. By contrast, in industrialized countries tetanus is now uncommon; however, cases have occurred in adults who have not previously been vaccinated or who have not received a booster dose.^{4,5}

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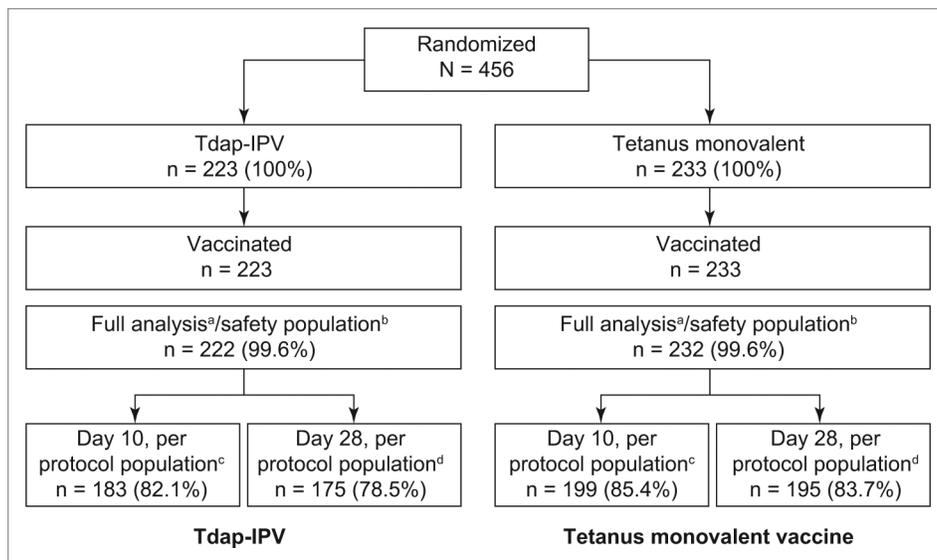


Figure 1. Flow of participants through the study. %, percentage based on the number of randomized participants: ^aFull analysis population: all randomized participants who received one of the study vaccines and with a post-vaccination immunogenicity evaluation. Participants were analyzed in the group to which they were randomized. ^bSafety analysis population: all participants who received one of the study vaccines and who had safety follow-up data. Participants were analyzed according to the study vaccine they actually received. In the Tdap-IPV group, one participant was lost to follow up and in the Tetanus monovalent group, one participant withdrew consent. Both withdrew before Day 10. ^cDay 10, per protocol population: all randomized participants excluding those with protocol violation(s) that may have interfered with the immunogenicity evaluation at Day 10. In both groups, 56 participants (12.3%) did not meet the inclusion criteria/met the exclusion criteria, 38 of them having received more than 1 tetanus-containing vaccine 5–10 y prior to study vaccine. In both groups, protocol violations were: at day 10, no post-vaccination immunogenicity data (n = 2); post-vaccination blood sampling out of day range (n = 3). ^dDay 28, per protocol population: all randomized participants excluding those with protocol violation(s) that may have interfered with the immunogenicity evaluation post-vaccination at Day 28. In both groups, these protocol violations consisted of: at Day 28, no post-vaccination immunogenicity data (n = 4); post-vaccination blood sampling out of day range (n = 9); received a non-study vaccine (n = 6).

Although effective childhood vaccination against pertussis had been widespread, a global epidemiological shift has been observed in older populations in the past 15 y,⁶ even in countries with high vaccination coverage of the disease. Adults, who currently do not receive a pertussis booster dose, are newly susceptible to the disease and when they are in contact with infants (e.g., if they are parents, grandparents or childcare and healthcare personnel), they are becoming the main source of infection.^{7–11} This can, therefore, critically impact susceptible young and not fully vaccinated infants, who are most at risk of pertussis life-threatening complications.⁸

Booster vaccination recommendations for adults differ from country to country: it is recommended every 10 y against tetanus and diphtheria (and poliomyelitis in France) in most European countries and in the US. Additionally, in France,¹² Germany¹³ and the US,¹⁴ a single dose of pertussis vaccine is recommended in adulthood.¹⁵ Other countries (e.g., Austria,¹⁶ Luxembourg¹⁷ and Norway¹⁸) recommend a pertussis booster every 10 y.¹⁵

Combined vaccines offer the opportunity to boost immunity against several infectious diseases simultaneously: the Tdap-IPV vaccine, REPEVAX® (Sanofi Pasteur MSD, Lyon, France) is a tetravalent vaccine that combines reduced-antigen diphtheria,

tetanus, acellular 5-component pertussis and inactivated poliomyelitis.¹⁹ Administration of a combination vaccine affords a good opportunity to optimize the efficiency of medical interventions among the general population.^{20–22}

Guidelines for the management of tetanus-prone injuries indicate that all patients who have received a tetanus-containing vaccine 5–10 y previously should receive an additional dose of tetanus toxoid. The Tdap-IPV vaccine might be an opportunity both to confer a rapid protection against tetanus in partially vaccinated adults^{3,7,13,23–25} and to boost immunity against several infectious diseases. The purpose of this study was to demonstrate that a Tdap-IPV vaccine would provide a non-inferior antibody seroresponse rate 10 d post-vaccination against tetanus toxoid, compared with a tetanus monovalent vaccine (TMV; Vaccin Tétanique Pasteur® or Tetavax®; Sanofi Pasteur MSD).

Results

A total of 458 adult subjects were screened and 456 subjects [173 men (37.9%) and 283 women (62.1)] with a mean age of 42.9 y, were randomized into the study (Fig. 1). One subject was

not randomized because of a known malignant disease, and the other subject was not randomized because the last booster of tetanus-containing vaccine was not received 5–10 y before administration of the study vaccine. The two treatment groups were comparable in terms of age, body mass index (BMI) and time since last booster vaccination (Table 1). The mean time since participants had received their last booster with a tetanus-containing vaccine was similar (roughly 7 y) in both groups (Table 1). At baseline, > 97% of the participants in both groups were seroprotected (anti-tetanus antibody concentration ≥ 0.1 IU/mL).

Immunogenicity endpoints. Primary endpoint. At Day 10, 100% of participants receiving Tdap-IPV and 99.0% of those receiving TMV had an anti-tetanus antibody concentration ≥ 0.1 IU/mL, confirming the non-inferiority of Tdap-IPV to TMV (Table 2).

Secondary endpoints. At Day 28, all participants receiving Tdap-IPV or TMV had anti-tetanus antibody concentrations ≥ 0.1 IU/mL. At Day 10 and Day 28 post-vaccination, geometric mean concentration (GMC) and geometric mean of individual concentration ratio (GMCR) were higher in the Tdap-IPV group than in the TMV group for the per protocol (PP) population (Fig. 2). Similar results were observed for the full analysis

population, supporting the results of the primary immunogenicity analysis (Table 2). At Day 10 post-vaccination, GMC and GMCR were higher in the Tdap-IPV group (12.2 IU/mL and 8.1, respectively) than in the TMV group (6.7 IU/mL and 4.5, respectively), based on non-overlapping confidence intervals (CIs). At Day 28 post-vaccination, the GMC and the GMCR remained higher in the Tdap-IPV group (10.6 IU/mL and 7.0, respectively) than in the TMV group (7.2 IU/mL and 4.8, respectively), based on non-overlapping confidence intervals.

Safety. Both Tdap-IPV and TMV were well-tolerated by participants and the frequency of adverse events was comparable between groups: 81.5% of participants in the Tdap-IPV group and 79.7% of those in the TMV group experienced at least one adverse event between Day 0 and Day 7 (Table 3). No adverse event led to the withdrawal of a participant from the study.

A similar number of participants in each group (76.6% of participants receiving Tdap-IPV and 74.6% receiving TMV) reported an injection-site reaction (mostly erythema, pain and swelling). Injection-site adverse events were mostly of mild or moderate (grade 1 or 2) intensity, occurred within 4 d of vaccination and lasted less than 8 d. One injection-site reaction (skin induration), which lasted more than 21 d, was considered by the investigator to be related to the vaccine (TMV group). Few participants experienced severe (grade 3) injection site reactions: one participant experienced a hematoma (> 10 cm, Tdap-IPV group), two participants an injection-site erythema (> 10 cm, Tdap-IPV group) and 12 participants (Tdap-IPV, n = 5; TMV, n = 7) severe (grade 3) injection-site pain.

Participants in the Tdap-IPV group had a numerically higher rate of systemic adverse events than participants in the TMV group [47.7% vs. 39.7%, respectively (descriptive statistics only)] (Table 3). The rates of unsolicited adverse events were similar in both groups (roughly 3.5%) but the rates of vaccine-related solicited adverse events were numerically higher in the Tdap-IPV group (myalgia 22.5%, headache 19.8%, malaise 8.1% and pyrexia 2.3%) compared with the TMV group (myalgia 14.2%, headache 11.6%, malaise 2.2% and pyrexia 0.4%) (Table 3). Systemic adverse events were mostly of mild or moderate (grade 1 or 2) intensity.

Among severe (grade 3) solicited vaccine-related adverse events, myalgia was the most common [5 (2.3%) vs. 6 (2.6%) participants receiving Tdap-IPV vs. TMV, respectively] followed by headache [3 (1.4%) vs. 3 (1.3%)] and malaise [3 (1.4%) vs. 0]. One participant in the Tdap-IPV group experienced pyrexia ($\geq 39^\circ\text{C}$ for 1 d at Day 0). Among the unsolicited severe (grade 3) adverse events asthenia, chills, influenza, rhinitis, tremor and cough were each reported once (Tdap-IPV group).

No serious adverse events were reported during the course of the study. One serious adverse event was reported after Day 28 in a 25-y-old woman who experienced a first episode of multiple sclerosis, 35 d after being vaccinated with Tdap-IPV. The causal relation between Tdap-IPV and multiple sclerosis was judged by the patient's neurologist and immunologist as "unknown" and by the investigator as "probably related to the study vaccine."

Table 1. Demographic characteristics of participants by treatment group allocation (Tdap-IPV vs. tetanus monovalent vaccine) (randomized population)

	Tdap-IPV (n = 223)	TMV (n = 233)	All participants (n = 456)
Age, mean \pm SD, years	42.3 \pm 16.6	43.4 \pm 18.4	42.9 \pm 17.5
Sex, n (%)			
Male	93 (41.7)	80 (34.3)	173 (37.9)
Female	130 (58.3)	153 (65.7)	283 (62.1)
BMI, mean \pm SD, kg/m ²	25.1 \pm 5.1	25.2 \pm 4.8	25.1 \pm 4.9
Time since last booster with tetanus-containing vaccine, mean \pm SD, years	7.3 \pm 1.5	7.4 \pm 1.5	7.3 \pm 1.5

BMI, body mass index; SD, standard deviation; TMV, tetanus monovalent vaccine.

Discussion

This study in adults with a known vaccination history demonstrates non-inferiority after 10 d of Tdap-IPV vaccine compared with TMV, with both vaccines inducing a strong, anti-tetanus antibody booster response. These results support the use of Tdap-IPV as a tetanus booster in the management of tetanus-prone injuries. Twenty-eight days after vaccination, seroprotection rates were 100% in both treatment groups, consistent with previous immunogenicity data for Tdap-IPV [seroprotection level ≥ 0.1 IU/mL in enzyme-linked immunosorbent assay (ELISA)].¹⁹

In a previous study comparing a tetanus monovalent vaccine with a combined Tdap vaccine, the observed percentage of sero-responders was lower than in the current study but was possibly related to vaccination history of the participants.²⁰ Our inclusion criteria were based on current tetanus-prone wound management recommendations in France.²⁶ These recommendations state that, for patients with major or contaminated wounds who have had a tetanus vaccine 5–10 y previously, a single booster injection of tetanus toxoid must be promptly administered on the day of injury.^{13,26}

Both Tdap-IPV and TMV were generally well-tolerated and participants in both groups experienced a similar incidence of injection-site reactions. The incidence of systemic events observed in the Tdap-IPV group is consistent with data reported in the Summary of Product Characteristics [SmPC; headache and myalgia reported as very common (frequency $\geq 10\%$) and pyrexia as common (frequency $\geq 1\%$ and $< 10\%$)] and with combination vaccines.²⁷ This is also consistent with data from a previous placebo-controlled study in healthy adults²⁸ and with those observed with combination vaccines.²⁷

Management of a tetanus-prone injury through vaccination using a combined vaccine such as Tdap-IPV provides an

Table 2. Pre- and post-vaccination geometric mean concentration, geometric mean concentration ratio and seroprotection rates to tetanus (IU/mL–ELISA) (full analysis population)

	Tdap-IPV (n = 222)			TMV (n = 232)		
	Pre-vaccination	Post-vaccination		Pre-vaccination	Post-vaccination	
		Day 10	Day 28		Day 10	Day 28
Anti-tetanus concentration (IU/mL)						
GMC	1.5	12.2	10.6	1.5	6.7	7.2
95% CI	1.3, 1.7	10.9, 13.7	9.5, 11.8	1.3, 1.7	5.9, 7.6	6.5, 7.9
Missing	0	0	2	0	0	0
Ratio post-/pre-vaccination						
GMCR	–	8.1	7.0	–	4.5	4.8
95% CI	–	7.1, 9.3	6.0, 8.1	–	4.0, 5.1	4.2, 5.5
Missing	–	0	2	–	0	0
Seroprotection rate (≥ 0.1 IU/mL)						
Participants, n (%)	218 (98.2)	222 (100.0)	220 (100.0)	226 (97.4)	230 (99.1)	232 (100.0)
95% CI	95.5, 99.5	98.4, 100	98.3, 100	94.5, 99.0	96.9, 99.9	98.4, 100
Seroprotection rate (≥ 0.1 IU/mL)*		n = 183*		n = 199*		
Participants, n (%)		183 (100)		197 (99)		
95% CI		98.0, 100.0		96.4, 99.9		
Estimate of difference [95% CI]: 1.0 [-1.2, 3.6]						
Non-inferiority: Yes						

GMC, geometric mean concentration; GMCR, geometric mean concentration ratio. *Per protocol population; primary outcome.

opportunity to improve vaccine coverage among the adult population by boosting immunity against several diseases including pertussis, simultaneously. An increasing incidence of pertussis has been observed in adolescents and adults, due to waning of vaccine immunity and lack of booster vaccination and natural boosting.^{29,30} As a result, incidence of pertussis has increased among vulnerable infants < 6 mo of age, who are too young to have completed their primary vaccination series.²⁹ The use of Tdap-IPV could, therefore, have multiple public health benefits including improvement of vaccine coverage through the re-introduction of antigens in an increasingly receptive adult population.

Materials and Methods

Study design and participants. This was a phase IIIb, multicenter, randomized, parallel group, open-label study (NCT00928785) conducted in France (four centers) and Germany (five centers) between July and December 2009. The study was conducted in accordance with national and local requirements and the protocol was approved by Independent Ethics Committees and by the Competent Authorities of each country. The Ethical Principles for Medical Research Involving Human Participants of the World Medical Association and the Declaration of Helsinki (World Medical Association, Inc. Available at: <http://www.wma.net/en/30publications/10policies/b3/index.html>) were adhered to. Written informed consent was obtained from all participants.

Healthy adults (aged ≥ 18 y) who had previously received a tetanus-containing vaccine 5–10 y prior to participation were enrolled in the study. Adults meeting the following criteria were excluded from the study: acute severe illness or fever ($\geq 38.0^\circ\text{C}$)

during the 72 h before vaccination; hypersensitivity or known allergy to one of the components of the study vaccines; serious allergic reaction (i.e., anaphylaxis) to a previous dose of a vaccine containing diphtheria or tetanus toxoids or poliomyelitis viruses or pertussis (acellular or whole cell); known encephalopathy after receipt of a pertussis vaccine or neurological disorders after an injection with the same antigens; Guillain-Barré syndrome or neuropathy of the brachial plexus following previous vaccination with a tetanus toxoid-containing vaccine; administration of blood products including immunoglobulins (≤ 90 d), live vaccine (≤ 28 d) or inactivated vaccine (≤ 14 d); or vaccination planned before the end of the study. Participants were also excluded from the study if they had a malignancy, were immunodeficient due to a medical condition or any other cause, had a positive pregnancy test before the first blood sample or were breastfeeding throughout the study period.

Participants were assigned to one of two groups to receive either the Tdap-IPV vaccine (REPEVAX[®]; Sanofi Pasteur MSD, manufactured by Sanofi Pasteur Ltd, Canada, Batch number D0250–2, also licensed as TRIAXIS POLIO[®] and ADACEL POLIO[®]) or the tetanus monovalent vaccine (TMV; Vaccin Tétanique Pasteur[®] or Tetavax[®]; Sanofi Pasteur MSD, Lyon, France, manufactured by Sanofi Pasteur SA, France, Batch number D5465–1). A central system provided a randomized allocation schedule using a 1:1 ratio based on balanced, permuted-block randomization and stratified by country. Study volunteers visited the investigator's site on three separate occasions: day of inclusion, randomization and vaccination (Day 0/Visit 1); Day 10 post-vaccination (Visit 2); Day 28 post-vaccination (Visit 3). A blood sample was taken at each visit. One dose (0.5 mL) of

Tdap-IPV or TMV was administered at Day 0 into the deltoid muscle. Both vaccines were presented as a suspension for injection in a pre-filled syringe for storage at 2.0–8.0°C.

All medications taken by the participant within 7 d prior to receiving study vaccination at Day 0/Visit 1, as well as all vaccinations, particularly any tetanus-containing vaccines given to the participant within 10 y prior to Day 0/Visit 1, were recorded in the electronic case report form (eCRF). Any concomitant medications and non-study vaccines (authorized or unauthorized by the study protocol) taken at Day 0 (day of vaccination) up to and including Day 28 were recorded in diary cards by the participant and reported in the eCRF by the investigator at the next visit.

Endpoints and assessments.

Serology assays were performed on blinded blood samples at Sanofi Pasteur. Anti-tetanus antibodies were measured by enzyme-linked immunosorbent assay at Day 0 (pre-vaccination), Day 10 and Day 28 post-vaccination. Immediate reactions following vaccination were monitored at Day 0 for 30 min. Solicited injection-site reactions (erythema, swelling and pain), systemic events [pyrexia (temperature $\geq 38.0^\circ\text{C}$), headache, malaise and myalgia] and unsolicited reactions or events (i.e., spontaneously reported) were recorded from Day 0 to Day 7. The subjects were requested to complete daily a diary card, which was reviewed by the investigator who checked for accuracy of the reported data and for any adverse event that could have been omitted by the subjects. Adverse events were described as mild (grade 1), moderate (grade 2) or severe (grade 3) in intensity. Serious adverse events (any untoward medical occurrence or effect that results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in a persistent or significant disability/incapacity, congenital anomaly/birth defect or another medically important event) were recorded from Day 0 to Day 28.

Statistics. Study power was calculated using the Farrington and Manning sample size formulae.³¹ It was assumed that there would be 205 evaluable participants in each group, that the true tetanus seroprotection post-vaccination [defined as the percentage of participants with anti-tetanus antibody titer (measured by ELISA) ≥ 0.1 IU/mL] at Day 10 would be 90% and that there would be no difference between treatment groups. Given these assumptions, this study had an overall power of 90.1% to show the non-inferiority of the Tdap-IPV group compared with the TMV group at the $\alpha = 0.025$ (one-sided) level. Estimates of the difference between the seroprotection rates between the groups (Tdap-IPV and TMV) were calculated, together with their

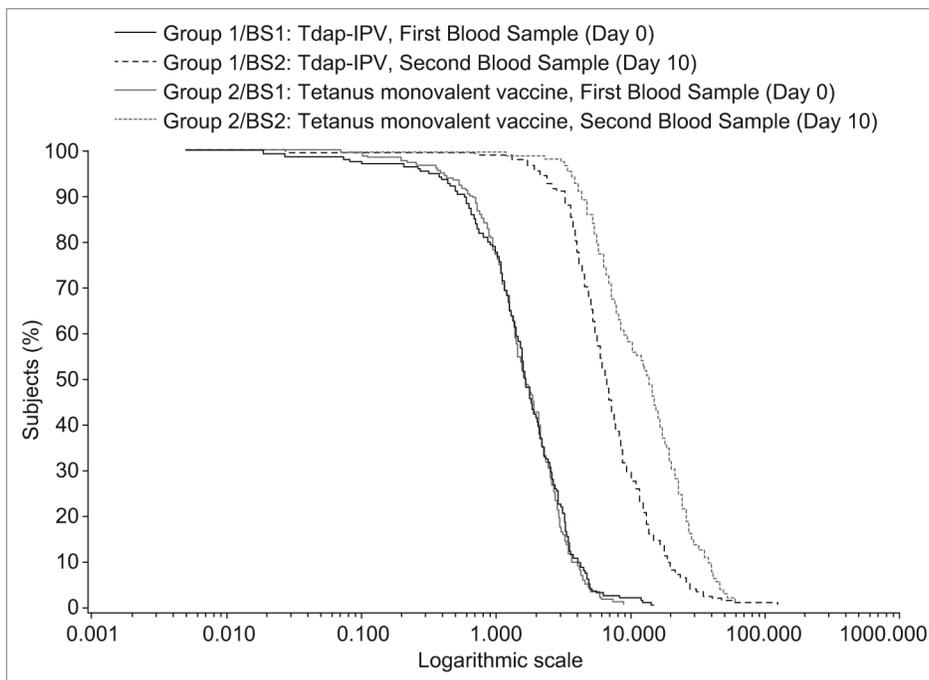


Figure 2. Reverse cumulative distribution of anti-tetanus concentration (IU/mL – ELISA), at day 10 (per protocol population).

Table 3. Adverse events occurring between Day 0 and Day 7 reported by participants receiving either Tdap-IPV or tetanus monovalent vaccine (full analysis population)

	Tdap-IPV (n = 222)	TMV (n = 232)
	<i>n (%)</i>	<i>n (%)</i>
Adverse events	181 (81.5)	185 (79.7)
Vaccine-related adverse events	177 (79.7)	181 (78.0)
Injection-site reactions	170 (76.6)	173 (74.6)
Solicited injection-site reactions	170 (76.6)	173 (74.6)
Erythema	39 (17.6)	46 (19.8)
Pain	165 (74.3)	169 (72.8)
Swelling	44 (19.8)	48 (20.7)
Unsolicited injection-site reactions	18 (8.1)	14 (6.0)
Systemic adverse events	106 (47.7)	92 (39.7)
Solicited systemic adverse events	92 (41.4)	70 (30.2)
<i>Vaccine-related solicited systemic adverse events</i>	73 (32.9)	51 (22.0)
Myalgia	50 (22.5)	33 (14.2)
Headache	44 (19.8)	27 (11.6)
Malaise	18 (8.1)	5 (2.2)
Pyrexia	5 (2.3)	1 (0.4)
Unsolicited systemic adverse events	34 (15.3)	35 (15.1)
<i>Vaccine-related unsolicited systemic adverse events</i>	8 (3.6)	8 (3.4)

TMV, tetanus monovalent vaccine.

two-sided 95% confidence intervals (CIs) based on the two-sample Wilson score method without continuity correction.³² If the lower boundary of the 95% CI of the difference was higher than -10% (i.e., the non-inferiority margin), it was concluded that Tdap-IPV was non-inferior to TMV. With up to 10% of participants expected to be non-evaluable for the primary analysis, due to withdrawals and protocol deviations, 228 participants were planned to be enrolled per group.

Immunogenicity was evaluated in the per protocol population, which included all participants without protocol deviations that might have interfered with the immunogenicity evaluation (main analysis), and in the full analysis population, which included all participants with any post-vaccination immunogenicity evaluation (supportive analysis). Descriptive statistics were provided for each group, including the geometric mean concentration and the geometric mean of individual concentration ratio (two-sided 95% CI) at Days 10 and 28, and the seroprotection rate (two-sided 95% CI) at Day 28 post-vaccination. Descriptive summaries were produced by group for all safety data.

Conclusions

Tdap-IPV is an appropriate combination vaccine that can substitute a monovalent tetanus vaccine, which is the current standard of care for prophylaxis of tetanus for wound management in an emergency setting. Tdap-IPV is well-tolerated, with an adverse event profile consistent with that observed with combination vaccines and with those described in the vaccine SmPC. A Tdap-IPV booster has the potential to optimize medical resources and vaccine coverage by allowing physicians to vaccinate against four major vaccine-preventable diseases simultaneously according to national guidelines.

Disclosure of Potential Conflicts of Interest

H.L. has received financial support for travel expenses to meetings in support of the study funded by Sanofi Pasteur MSD. U.Z. has no conflicts of interest to declare. F.G. has received a consulting fee from Sanofi Pasteur MSD which was given to her institution [INSERM, Réseau National d'Investigation Clinique en Vaccinologie (REIVAC), France and CHRU Montpellier, Hôpital St Eloi]. O.L. has received a grant for clinical studies which was given to her institution [Assistance Publique-Hôpitaux de Paris (AP-HP), Hôpital Cochin] and has received travel support from Sanofi Pasteur MSD and other companies to attend scientific meetings. X.D. has received a consulting fee from Sanofi Pasteur which was given to his institution (Bichat Claude Bernard Hospital) and has received funds for travel/accommodation/meeting expenses from GSK and Roche. He has a research grant pending from Gilead Pharmaceuticals. P.R., C.S. and B.S. are employees of Sanofi Pasteur MSD.

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Transparency declaration

H.L. and O. L. are members of "Avancées Vaccinales" sponsored by Sanofi-Pasteur. O. L. is an investigator on vaccine studies sponsored by Sanofi Pasteur MSD and other companies, and has received travel support from Sanofi Pasteur MSD and other companies to attend scientific meetings. This study was sponsored by Sanofi Pasteur MSD.

Author contributions

H.L. and F.G. were responsible for patient enrolment and study data analysis and interpretation. U.Z. was responsible for laboratory data acquisition and patient enrolment. Odile Launay was responsible for study conception and design, patient enrolment and study data analysis and interpretation. X.D. was responsible for laboratory data acquisition, patient enrolment and data analysis and interpretation. P.R. and C.S. were responsible for study conception and design and data analysis and interpretation. B.S. was responsible for study conception and design. All authors reviewed the first draft, critically revised the manuscript for important intellectual content and provided final approval of the version to be published.

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